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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/232,290	01/15/99	FLUCK THUN A	MORPHO/7

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EXAMINER	
DELOUX, A	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/232,290	Pluckthun, A et al.
Examiner	**Art Unit**
DeCloux, Amy	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 12, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5 and 7-27* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5 and 7-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☑ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

2. Applicant's amendment, filed 3/12/2001 (Paper No. 19) is acknowledged and has been entered.

Claims 1-5 and 7-27 are pending and are being examined presently.

3. The rejections of record can be found in the Final Office Action, mailed 12/5/00 (Paper No. 18). In view of applicant's amendment and Remarks, filed 3/12/2001 (Paper No. 19) , the outstanding 112 first rejection has been withdrawn. However, the art rejections have been maintained. Also a new grounds of rejection has been applied.

4. The following order or arrangement is preferred in framing the specification and, except for the title of the invention, each of the lettered items should be preceded by the headings indicated below.

(a) Title of the Invention.
(b) Cross-References to Related Applications (if any).
(c) Statement as to rights to inventions made under Federally-sponsored research and development (if any).
(d) Background of the invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under *37 C.F.R. §§ 1.97-1.99.*
(e) Summary of the Invention.
(f) Brief Description of the Drawing.
(g) Description of the Preferred Embodiment(s).
(h) Claim(s).
(I) Abstract of the Disclosure.

5. The disclosure is objected to because of the following minor informalities:

A) there appears to be a misspelling of "superfamily" on page 6, line 6 of the instant specification ,

B) there appears to be an unfinished sentence on page 19, line 4 of the instant specification.

6. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It is not clear how the limitation of claim 7 which recites that said domain or fragment is derived from an antibody, further limits claim 1 since claim 1 already recites said limitation. Applicant is invited to clarify.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

8. Claims 1-5 and 7-27 are rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A. Claim 1 and dependent claims 2-5 and 7-27 are indefinite in the recitation of "an interface" in line 1 of part a of said claim because it is not clear if the phrase is referring to the exposed interface of line 3 of claim 1.

B. Claim 12 is indefinite in the recitation of "interface region" because said phrase lacks antecedent basis.

C. Claim 1 dependent claims 2-5 and 7-27 are indefinite in the recitation of the phrase "as compared to" in lines 2-3 of part b of said claim because it is not clear how said phrase relates to the preceding term "modification" and the following term "a domain or fragment of a parent antibody". Perhaps applicants could substitute "of" for the phrase "as compared to".

D. Claims 4 and 5 are indefinite in the recitation of the phrase "more hydrophillic" in part a of said claim because it is not clear what the object of comparison is.

9. Regarding the outstanding 102(b) and 103 rejections, applicant argues that the definition of "interface" used by Johnson et al is different from that of the instant specification because the VL VH interface in Johnson is not between "contiguously adjoined" domains as recited in applicant's amended claim 1 but instead exists between distinct polypeptides. Examiner agrees in part and notes that on page 10 (lines 16-28) of Johnson et al it is taught to examine residues located at the interface of the heavy and light chains domains of an immunoglobulin. However it is noted by the examiner that Johnson et al may also encompass an interface that allows contact along a longitudinal axis between adjacent domains within a heavy chain or within a light chain of a larger antibody or antibody fragment, since Johnson et al also teaches in the last paragraph of page 12 and the first paragraph of page 13 that examples include Fab scFv and Fv fragments, all which are also recited in the applicant's claims 8, 9, 10 and 11. Therefore Applicant further asserts that applicant's amended claims do not

encompass an interface between immunoglobulin domains derived from different chains (IE VH from the heavy chain and VL from the light chain). However since applicants have not altered claims 1 and 10 that encompass scFv, and since there is no such exclusitory language in claim 1, applicant's amended claims do encompass an interface between immunoglobulin domains derived from different chains (IE VH from the heavy chain and VL from the light chain).

The examiner also notes that the instant specification discloses on page 3 that Johnson et al teaches that isolated single domains, e.g. VH, can be modified in the former VL/VH interface region by exchanging hydrophobic residues by hydrophilic ones, and this teaching anticipates claim 1 and dependent claims 9 and 11 since the latter two claims recited an Fv fragment.

Note: Applicant is invited and encouraged to further differentiate applicant's invention from that of Johnson et al so that allowable subject matter can be determined. Therefore, although applicant's arguments have been carefully considered, they are deemed unpersuasive and the 102(b) and 103(a) rejections are maintained.

10. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-5, 7-11, 13-17, and 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al (WO 92/01787)(IDS).

Johnson et al teach an analogue of a single chain variable domain of a member of an immunoglobulin, in which said analogue one or more interface amino acid residues of the domain is altered, wherein the said altered amino acid is substituted with a residue so that the analog is more hydrophilic than the unaltered domain, (see entire patent, especially pages 6 and 7, last and first paragraph, respectively) and teaches that said analogues are obtained using site directed mutagenesis and a recombinant expression system, (see entire patent, especially pages 9-10) as recited in the instant Claims 1 and 26-27. Johnson et al teach that said analogues comprising domains which are synthetic analogs of a natural single variable domain of a member of an immunoglobulin superfamily (see entire patent, especially page 1, lines 6-9) such as single chain variable domains (see entire patent, especially page 19).

With regard to claims 2-7 and 10, Johnson et al teach that said alteration of a single chain variable domain of a Fab, Fv, scFv or immunoglobulin isotype (page may be by way of amino acid substitution, deletion, addition inversion, (see entire article,

especially page 7, lines 12-15) and the amino acids substituted include Q, T E D S G or N (see entire patent, especially pages 7 and 8). With regard to claims 13-14, Johnson et al teach said single chain moieties may be further coupled an additional moiety that can be enzymic, florescent, radiolabeled or a portion of an immunoglobulin (see entire patent, especially page 8, lines 17-21). With regard to claims 15-17, Johnson et al also teaches cloning the recombinant products into fd phage (see entire patent, especially page 20 , line 1) and also that said analog or derivative can be displayed on a phage as a fusion with gene III protein of filamentous bacteriophage (see entire patent, especially page 20 , lines 15-23).

Therefore, the reference teachings anticipate the claimed invention

12. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-5, 7, 10-11, 13-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al (WO 92/01787)(IDS) in view of Jenkins et al (PNAS 92:6057-6061, 1995)(IDS) and Knappik et al (Biotechniques 17(4):754-761, 1994) and Dubel et al. (J. Of Immunological Methods 178:201-209, 1995) and Kostelny et al (Journal of Immunology 148:1547-1553, 1992).

Johnson et al teaches as above, however Johnson et al does not teach a DNA sequence with an additional moiety capable of binding a metal ion, as recited in claims 18-19, or a peptide or labeling tag moiety as recited in claims 20-22.

Jensen et al teaches DNA recombinant methods of producing mutants of the HIV

integrase gene by replacing hydrophobic residues to increase its solubility (see page 6060, column 2, third paragraph of Discussion section). Jensen et al also teaches that the recombinant methods include the use of a histidine tag that allows rapid purification of the expressed protein on a nickel chelating column (see entire article, especially page 6057, column 2, last paragraph).

Knappik et al teaches that the FLAG peptide has been successfully used as a detection and purification tag of antibody fragments expressed in E. Coli (see entire article, especially page 761, column 1, first sentence).

Dubel et al teach bifunctional and multimeric complexes scFv antibodies containing various coupling sites by adding streptavidin and a single cysteine to the C terminus of the scFv antibody in order to produce multispecific as well as multivalent scFv complexes (see entire article, especially page 202, column 1). Dudel et al also teach that said coupling would facilitate the creation of complexes with other antibodies or effector molecules for use in therapeutic strategies (see entire article, especially page 202, column 1).

Kostelny et al teach a DNA sequence comprising leucine zipper regions linked to the Fab' portion of each of two monoclonal antibodies, each being expressed as homodimers. However when these homodimers were reduced at the hinge region to form monomers and then reoxidized together, heterodimeric end products were produced. Kostelny et al also teach that said molecules are valuable in immunotherapy. (See entire article including the Abstract and page 1547).

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have made and used a DNA sequence as recited in Claims 1-7, 10, 13-17, and 26-27 in view of the teachings of Johnson et al. for the reasons stated in the above 102b rejection in Section 11 of this office action.

With regard to claims 18-22, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have made and used a DNA sequence that encoded a modified antibody or antibody fragment as taught by Johnson et al that had an additional moiety of a histidine tag as taught by Jensen et al, or an additional moiety of a FLAG peptide as taught by Knappik et al because both Jensen et al and Knappik et al teach that said moieties aid in the detection and purification of expressed proteins, especially antibody fragments, and one would expect that it would also aid in the detection of recombinant mutants of said antibody fragments.

With regard to claims 1, 13, 20, 23 and 25, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have made and used a DNA sequence as taught by Johnson et al that encoded an antibody or antibody fragment coupled to streptavidin and a single cysteine to the C terminus of the scFv antibody in order to produce multispecific as well as multivalent scFv complexes taught

by Knappik et al because Knappik et al teach that said coupling facilitates the creation of complexes with other antibodies or effector molecules for use in therapeutic strategies.

With regard to claims 1, 13, 20, 23-25, it would have been obvious to one of ordinary skill in the art at the time the invention who wanted to use an antibody with dual specificity in immunotherapy was to have made and used a DNA sequence as taught by Johnson et al that encoded an antibody fragment that was linked to a leucine zipper, since Kostelny et al also teach that said molecules are valuable in immunotherapy.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claim 12 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. a message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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June 18, 2001

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